DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

May 2, 2009

Richard E. Besser, MD
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Centers for Disease Control and Prevention
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Dear Dr. Besser:

This letter is in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of the CDC[1] Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel for Respiratory Specimens (**NPS, NS, TS, NPS/TS, NA**[2]) and Viral Culture (rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**)) as a first tier test for the qualitative detection of influenza virus type A or B and subtype determination of seasonal human influenza A virus (seasonal A/H1 or A/H3) for individuals suspected of having a 2009 H1N1 influenza virus infection, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3) by public health and other qualified laboratories.

The CDC Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel (rRT-PCR Flu Panel) was cleared by FDA on September 30, 2008 for use with nasopharyngeal and/or nasal swab specimens. Because of issues of availability and adequacy of the cleared test associated with the need for testing additional specimen types, this letter authorizes the emergency use of the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) with specimen types and reagents in addition to those of the cleared test, as described below. The rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) is authorized as a first tier test for patient specimens with suspected 2009 H1N1 influenza virus and is an integral component of the testing algorithm for the rRT-PCR Swine Flu Panel authorized for use under an April 27, 2009 Emergency Use Authorization.

On April 26, 2009, pursuant to section 564(b)(1)(C) of the Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency under 42 U.S.C. § 247d that affects, or has a significant potential to affect, national security, and that involves a specified biological, chemical, radiological, or nuclear agent or agents, or a specified disease or condition that may be attributable to such an agent or agents -- in this case, 2009 H1N1 influenza virus.[3] Pursuant to section 564(b) of the Act (21 U.S.C. § 360bbb-3(b)), and on the basis of such determination, the Secretary of the Department of Health and Human Services then declared an emergency justifying the

[1] Centers for Disease Control and Prevention
[2] Nasopharyngeal swabs, nasal swabs, throat swabs, dual nasopharyngeal swabs/throat swabs, nasal aspirates.
[3] Memorandum, Determination Pursuant to § 564 of the Federal Food, Drug, and Cosmetic Act (April 26, 2009).

authorization of the emergency use of the CDC Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel for Respiratory Specimens (**NPS, NS, TS, NPS/TS, NA**) and Viral Culture subject to the terms of any authorization issued under 21 U.S.C. § 360bbb-3(a).

Having concluded that the criteria for issuance of this authorization under section 564(c) of the Act (21 U.S.C. § 360bbb-3(c)) are met, I am authorizing the emergency use of the CDC Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel for Respiratory Specimens (**NPS, NS, TS, NPS/TS, NA**) and Viral Culture (rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**))[4] as a first tier test for the qualitative detection of influenza virus type A or B and subtype determination of seasonal human influenza A virus (seasonal A/H1 or A/H3) in individuals suspected of having a 2009 H1N1 influenza virus infection. The rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) is a first tier test because it should be used to test specimens from such individuals first. If the test result of the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) is positive for influenza A and negative for H1 (seasonal) and H3 subtypes, then the laboratory should test the specimen with the rRT-PCR Swine Flu Panel.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) as a first tier test for the qualitative detection of influenza virus type A or B and subtype determination of seasonal human influenza A virus (seasonal A/H1 or A/H3) for individuals suspected of having a 2009 H1N1 influenza virus infection meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

(1) The recently isolated novel 2009 influenza A (H1N1), or swine flu, virus can cause influenza, a serious or life threatening disease or condition to humans infected by this virus;

(2) based on the totality of scientific evidence available to FDA, it is reasonable to believe that the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) may be effective as a first tier test for the qualitative detection of influenza virus type A or B and subtype determination of seasonal human influenza A virus (seasonal A/H1 or A/H3) in nasopharyngeal swabs (NPS), nasal swabs (NS), throat swabs (TS), and/or dual NPS/TS swab specimens and nasal aspirates (NA) from patients with signs and symptoms of respiratory infection suspected of having a 2009 H1N1 influenza virus infection and/or from viral culture, and that the known and potential benefits of the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**), when used as a first tier test in the qualitative detection of influenza virus type A or B and subtype determination of seasonal human influenza A virus (seasonal A/H1 or A/H3), outweigh the known and potential risks of such products; and

(3) there is no adequate, approved, and available alternative to the emergency use of the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) as a first tier test for the qualitative detection of influenza virus type A or B and subtype determination of seasonal human

[4] FDA is authorizing the emergency use of the CDC Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel for Respiratory Specimens (**NPS, NS, TS, NPS/TS, NA**) and Viral Culture (rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) as described in the scope section of this letter (Section II). For ease of reference, this letter will use the term the " rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**)."

influenza A virus (seasonal A/H1 or A/H3) in nasopharyngeal swabs (NPS), nasal swabs (NS), throat swabs (TS), and/or dual NPS/TS swab specimens and nasal aspirates (NA) from patients with signs and symptoms of respiratory infection and/or from viral culture specimens suspected of having a 2009 H1N1 influenza virus infection.[5]

Therefore, I have concluded that the emergency use of the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) as a first tier test for the qualitative detection of influenza virus type A or B and subtype determination of seasonal human influenza A virus (seasonal A/H1 or A/H3) for individuals suspected of having a 2009 H1N1 influenza virus infection meets the above criteria for issuance of an authorization.

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) for the qualitative detection of influenza virus type A or B and subtype determination of seasonal human influenza A virus (seasonal A/H1 or A/H3) for individuals suspected of having a 2009 H1N1 influenza virus infection.

The authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**):

CDC Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel for Respiratory Specimens (**NPS, NS, TS, NPS/TS, NA**) and Viral Culture is a panel of oligonucleotide primers and dual-labeled hydrolysis probes for use in the real-time RT-PCR assay on the ABI 7500 Fast Dx Real-Time PCR instrument for the *in vitro* qualitative detection of human influenza viral RNA in nasopharyngeal swabs (NPS), nasal swabs (NS), throat swabs (TS), and/or dual NPS/TS swab specimens and nasal aspirates (NA) from patients with signs and symptoms of respiratory infection and/or from viral culture.[6]

The rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) uses the same primer and probe sequences as the CDC Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel as the device cleared under K080570 except that the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) authorized for emergency use also utilizes the AgPath-ID™ One-Step RT-PCR Kit Human amplification reagents.

Assay principle

- The rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) is used in real-time RT-PCR assays on the ABI 7500 Fast instruments. The primer and probe sets are designed for detection and subtyping of influenza A viruses.

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[5] The cleared test for *in vitro* qualitative detection of human influenza viral RNA (The CDC rRT-PCR Flu Panel (IVD) 510(K) 080570) is not adequate because of the need to test additional types of samples during this emergency and it is not sufficiently available because of limited availability of certain reagents. No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

[6] The CDC rRT-PCR Flu Panel (IVD) 510(K) 080570 is indicated for the *in vitro* qualitative detection of human influenza viral RNA in nasopharyngeal swabs (NPS) and nasal swabs (NS) only.

- One-step RT-PCR assays are one-tube assays that first reverse-transcribe specific Ribonucleic acid (RNA) templates into cDNA copies. The complementary deoxyribonucleic acid (cDNA) then undergoes a polymerase chain reaction (PCR) that utilizes a thermocyclic heating and cooling of the reaction to logarithmically amplify a specific region of DNA. The probe anneals to a specific target sequence located between the forward and reverse primers. During the extension phase of the PCR cycle, the 5' nuclease activity of Taq polymerase degrades the probe, causing the reporter dye to separate from the quencher dye, generating a fluorescent signal. With each cycle, additional reporter dye molecules are cleaved from their respective probes, increasing the fluorescence intensity. Fluorescence intensity is monitored at each PCR cycle.

- No template controls (NTCs) and positive template controls for all primer and probe sets are included in each run. An extraction control (HSC) provides a secondary negative control that validates the extraction procedure and reagent integrity. The RNase P assay serves as a control to ensure adequate RNA resulted from extraction of each clinical specimen and that no inhibitors were present in the specimen. RNA extracted from clinical samples contains human RNA. The RP primer and probe set targets the human ribonuclease P gene. Therefore, the level of the RNase P primer and probe set reaction reflects the relative amount of human RNA recovered from the specimen and its suitability for clinical testing.

The above rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**), when labeled consistent with the attached template, is authorized to be distributed to public health and other qualified laboratories[7] under this EUA, despite the fact that it does not meet certain requirements otherwise required by federal law.

The following written information pertaining to the emergency use of the authorized rRT-PCR Swine Flu Panel is authorized to be made available to health care providers and patients:

- Fact Sheet For Healthcare Providers: Interpreting rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) Test Results
- Fact Sheet For Patients: Understanding rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) Kit Test Results

See attached. As described in section IV below, CDC and the appropriate state and/or local public health authority(ies) are also authorized to make available additional information relating to the emergency use of the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) that is consistent with, and does not exceed, the terms of this letter of authorization.

I have concluded, pursuant to section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**)

[7] All users, analysts, and any person reporting diagnostic results from use of this device should be trained to perform and interpret the results from this procedure by a CDC instructor or designee prior to use. CDC Influenza Division will limit the distribution of this device to those users who have successfully completed training provided by CDC instructors or designees. Use is limited to designated laboratories that are qualified to receive and use the CDC rRT-PCR Flu Panel (IVD) 510(K) 080570. See "Conditions of Authorization" below.

in the specified population, when used as a first tier test in the qualitative detection of influenza virus type A or B and subtype determination of seasonal human influenza A virus (seasonal A/H1 or A/H3) for individuals suspected of having a 2009 H1N1 influenza virus infection, outweigh the known and potential risks of such product.

I have concluded, pursuant to section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) may be effective as a first tier test in the qualitative detection of influenza virus type A or B and subtype determination of seasonal human influenza A virus (seasonal A/H1 or A/H3) for individuals suspected of having a 2009 H1N1 influenza virus infection pursuant to section 564(c)(2)(A) of the Act. FDA has reviewed the scientific information available including the information supporting the conclusions described in Section I above, and concludes that the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**), when used for qualitative detection of influenza virus types A or B and subtype determination of seasonal human influenza A virus (seasonal A/H1 or A/H3) from individuals suspected of having a 2009 H1N1 influenza virus infection in the specified population, meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) under this EUA must be consistent with, and may not exceed, the terms of this letter, including the scope and the conditions of authorization set forth below. Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) described above is authorized as a first tier test to qualitatively detect influenza virus types A or B and subtype seasonal human influenza A virus (seasonal A/H1 or A/H3) for individuals suspected of having a 2009 H1N1 influenza virus infection.

This EUA will cease to be effective when the declaration of emergency is terminated under section 564(b)(2) of the Act or when the EUA is revoked under section 564(g) of the Act.

III. Waiver of Certain Requirements

I am waiving the following requirements for the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) during the duration of this emergency use authorization[8]:

- current good manufacturing practice requirements, including the quality system requirements under 21 CFR Part 820 with respect to the design, manufacture, packaging, labeling, storage, and distribution of the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**);
- registration and listing requirements under section 510 of the Act;
- labeling requirements for cleared, approved, or investigational devices, including labeling requirements under 21 CFR 809.10 and 809.30, except for the intended use statement (21 CFR 809.10(a)(2), (b)(2)), adequate directions for use (21 U.S.C. 352(f)), (21 CFR 809.10(b)(5) and (8)), any appropriate limitations on the use of the device including information required under 21 CFR 809.10(a)(4), and any available information

[8] These requirements are waived only for the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) that is authorized for emergency use. These requirements, and all other applicable statutory and regulatory requirements, continue to apply to the CDC rRT-PCR Flu Panel (IVD) 510(K) 080570.

regarding performance of the device, including requirements under 21 CFR 809.10(b)(12);
- investigational device requirements, including requirements under 21 CFR Part 812; and
- reporting requirements that apply to cleared or approved devices, including requirements under 21 CFR Parts 803 and 806.

IV. Conditions of Authorization

Pursuant to section 564 of the Act, I am establishing the following conditions on this authorization:

CDC

A. CDC will distribute the rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) labeled with the intended use statement, adequate directions for use, any appropriate limitations on the use of the device, and any available information regarding performance of the device only to qualified laboratories.

B. CDC will provide to the qualified state and/or local public health authority(ies) the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) Fact Sheets for health care providers, and the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) Fact Sheets for patients.

C. CDC will make available on its website the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) Fact Sheets for health care providers, and the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) Fact Sheets for patients.

D. CDC will ensure that the state and/or local public health authority(ies) are informed of this EUA, including the terms and conditions herein.

E. CDC will ensure qualified laboratories have a process in place for reporting test results to health care providers and federal, state and/or local public health authorities, as appropriate.

F. CDC will track adverse events.

G. Through a process of inventory control, CDC will maintain records of device usage.

H. CDC will collect information on the performance of the assay, to include the incidence of false positive results.

Public Health and Other Qualified Laboratories

I. Qualified laboratories will perform the assay on an Applied Biosystems 7500 Fast Dx Real-time PCR instrument or the RUO marketed Applied Biosystems 7500 Real-time PCR instrument that is validated by Applied Biosystems with regard to the updated software but only partially qualified regarding its laboratory performance (proficiency testing with the CDC sample panel not performed).

J. Qualified laboratories will have a process in place for reporting test results to health care providers and federal, state and/or local public health authorities, as appropriate.

CDC and State and/or Local Public Health Authority(ies)

K. CDC and the appropriate state and/or local public health authority(ies) are authorized to make available additional information relating to the emergency use of the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) that is consistent with, and does not exceed, the terms of this letter of authorization.

L. Only CDC may request changes to the authorized Fact Sheet for health care providers or the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) Fact Sheet for patients. Such requests will be made by contacting FDA concerning FDA review and approval.

M. CDC and the appropriate state/and or local public health authority(ies) will ensure that records associated with this EUA are maintained until notified by FDA. Such records will be made available to FDA for inspection upon request.

The emergency use of the authorized rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) as described in this letter of authorization must comply with the conditions above and all other terms of this authorization.

V. Duration of Authorization

This EUA will be effective until the declaration of emergency is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

5/2/19

Joshua M. Sharfstein, MD
Principal Deputy Commissioner
Acting Commissioner

Attachments

1. Fact Sheet For Healthcare Providers: Interpreting rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) Test Results
2. Fact Sheet For Patients: Understanding rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) Test Results
3. CDC Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel for Respiratory Specimens (**NPS, NS, TS, NPS/TS, NA**) and Viral Culture (rRT-PCR Flu Panel (**NPS, NS, TS, NPS/TS, NA**) labeling.